A Synopsis of the Thesis entitled

"Design Synthesis and Biological Activity Evaluation of Novel Sulphur Containing Heterocyclic Compounds"

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Submitted by

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Abstract

From many decades, S-heterocycles have maintained their status as an important part and core of FDA approved drugs and medicinally active compounds. With exhaustive exploration of sulphur heterocycles in medicinal chemistry, researchers have shifted their interest towards other heterocycles, especially, S-heterocycles. Thus several attempts have been made to synthesize a variety of new sulphur containing compounds with high medicinal value and low toxicity profile, in comparison to previous S-heterocycles. Till today, S-heterocycle containing compounds have been largely reported as anticancer, antidiabetic, antimicrobial, antihypertension, antiviral, anti-inflammatory etc. In this review, the authors have tried to provide a critical analysis of synthesis and medicinal attributes of sulphur containing heterocycles such as thiirane, thiophene, thiazole, thiopyran, thiazolidine etc reported within last five years to emphasize the significance and usefulness of these S-heterocycles in the drug discovery process.

Aim of study:

To design and synthesis structurally diverse heterocyclic compounds containing one or two hetero-atom and their biological activity evaluation towards discovery of potent drug candidate.

Objectives of study:

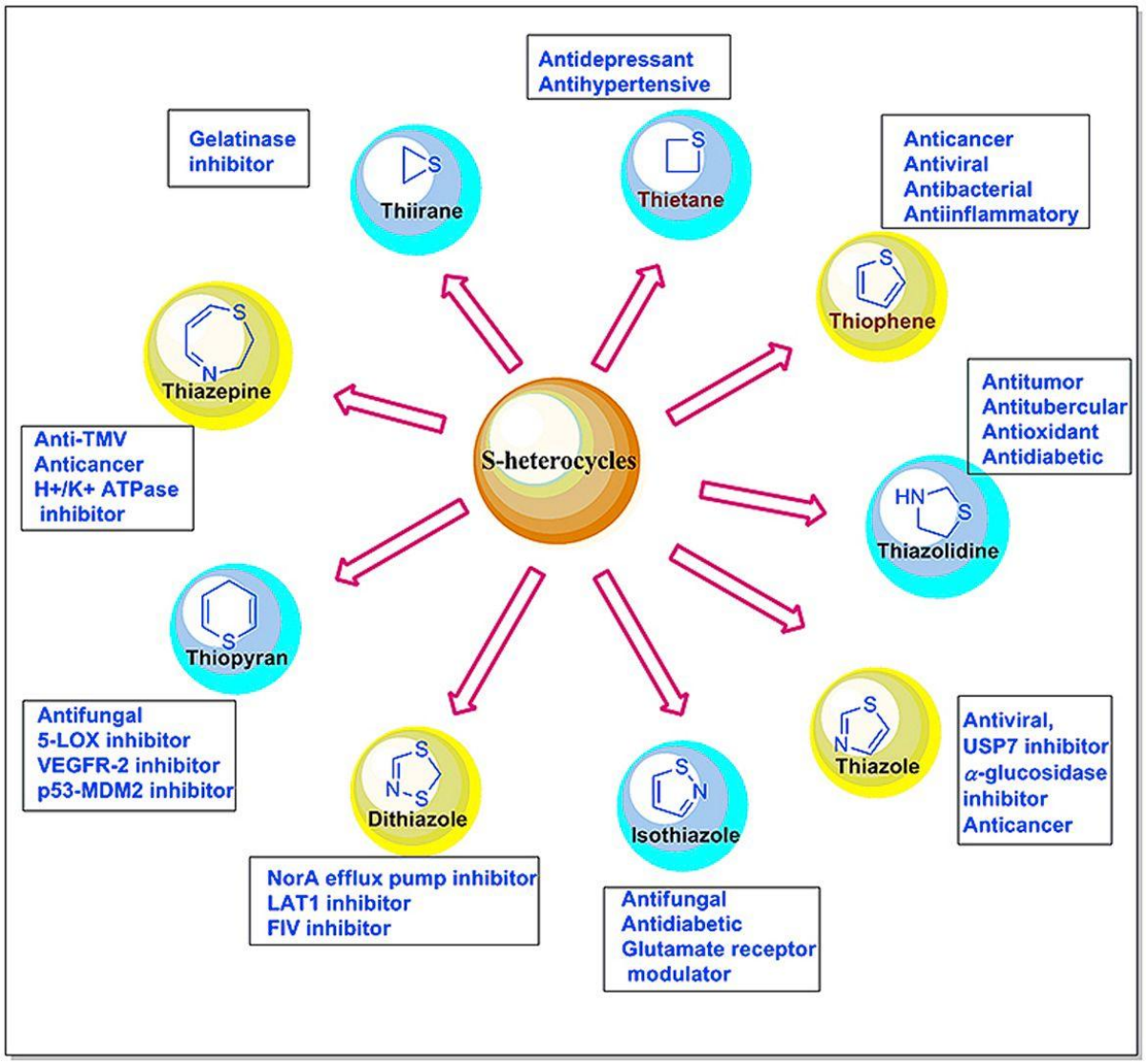
- To develop novel synthetic method for sulphur containing heterocycles.
- Synthesis of different derivatives of sulphur containing heterocycles.
- Characterization of synthesized material using different sophisticated techniques such as 1H NMR spectroscopy, 13C NMR spectroscopy, Mass spectrometry, IR spectroscopy, 2-D NMR spectroscopy, etc.
- Bio-evaluation of synthesized sulphur containing heterocyclic compounds against different strains to find more potent drug molecules.

Introduction

Almost every person of the population suffers with many diseases, so there is a dire need for the development of new and potent medicinal compounds. Researchers made a lot of effort for the designing of new drugs either by exploring the existing lead compounds or finding a new biological target, so that every ailment can be cured and treated. Many heterocyclic moieties form the core structure of clinically used drugs thus revealing the importance of heterocycles in the development of novel pharmacologically active compounds . Heterocycles containing sulphur as heteroatom (S-heterocycles) are one of the most important class among other heterocyclic compounds that are continuously utilized in the field of chemistry . Several sulphur containing scaffolds exist in various natural compounds and drugs which serve as biologically active molecules in various pathophysiological conditions . Additionally, due to highly volatility and reactivity of sulphur, many sulphur containing compounds also have role in flavoring of food products such as vegetables, meat, and roasted products like coffee, cocoa, and peanuts . Sulphur containing heterocycles exhibited many pharmacological actions like anticancer, antiviral, anti-inflammatory, antimicrobial, antitubercular etc. The most common sulphur containing heterocycles explored in the drug designing belong to five, six, seven membered rings including thiazole, isothiazole, thiophene, thiopyran, thiazolidine and thiazepine . Several FDA approved drugs are available which possess sulphur heterocycles including Raloxifene , a well-known drug for the treatment of breast cancer, Clopidogrel , used to treat peripheral artery disorders, Ritonavir , a potent antiviral agent, Rosiglitazone , clinically used for the treatment of diabetes and Thiabendazole , as an antifungal drug. Many more drugs constitute the list of FDA approved S heterocycles based therapeutic agents.

Thus, indicating the importance of sulphur containing heterocycles in the designing of small molecules with potent biological activity. Our research group has also carried out significant work in the area of sulphur heterocycles, especially on the thiazolidinone moiety. Various thiazolidinone derivatives have been synthesized , evaluated for antiviral activity against many viruses including human immunodeficiency virus type 1 (HIV-1) , Hepatitis C virus (HCV) NS5B RNA polymerase. Molecular docking, QSAR studies have been also performed for various thiazolidinone derivatives. Recently, Colovic et al. published an article that focused on the defensive effects of various sulphur containing amino acids against free radicals and heavy metals. Another most recent article was published by Sharma et al. on thiazole related derivatives which covers their therapeutic importance especially from the patents filed between 2000 and 2017. Here, in this review article we have focused on all S heterocycles moiety rather

than on particular individual moiety. Authors have attempted to provide an overview of the various synthetic routes employed to develop biologically rich sulphur based scaffolds as well as the reactions these nucleus undergo to yield various other important molecules. It also highlights the recently reported (mainly last five years) therapeutic properties of the developed molecules and the list of various sulphur containing FDA approved marketed drugs. This compilation highlights the significance for further research work on the bioactive sulphur containing molecules.



Literature review and recent developments in the field

Heterocycles play a vital role in pharmacological, agricultural and synthetic fields. Consequently, the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. S-heterocyclic compound unit constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds and display a wide range of biological activity. Survey of literature revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity was produced. The chemistry of these linked heterocyclics has been a fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profile.

The review of literature concerned to S-heterocyclic compound revealed that S-heterocyclic compound coupled heterocycles are displaying better activity. Many S-heterocyclic compound substituted heterocycles have been synthesized and studied for their pharmacological activity. From the review, it is clear that a number of S-heterocyclic compound derivatives are finding applicability in the chemotherapy. Synthesis and biological evaluation of S-heterocyclic compound substituted heterocycles is a fast-developing area, hence we are fascinated to synthesize a number of S-heterocyclic compound heterocycles to evaluate their antimicrobial properties.

Study background (Literature survey) and significance of study:

Heterocyclic compounds are of chemical, biomedical and industrial significance. Sulphur heterocycles are part of many biologically important compounds such as alkaloids, nucleic acids, amino acids, proteins, drug molecules, etc. Due the wide applications of sulphur containing heterocyclic compounds, worldwide scientific community attracted towards their synthesis.

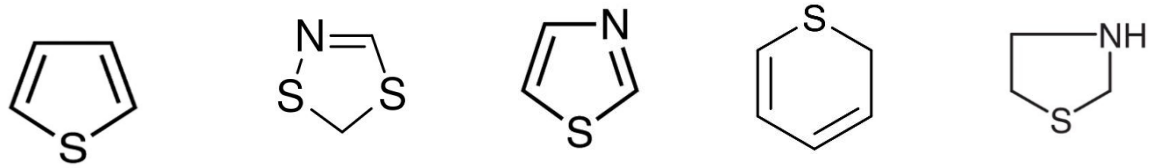


Figure 1: Thiophene *Figure 2 Dithiazole* *Figure 3 Thiazaole* *Figure 4 Thiopyran* *Figure 5 Thiazolidine*

Fig. 1 Some examples of important sulphur heterocycles

Study hypothesis

Heterocyclic compounds are having various biological properties. Among the heterocyclic compounds, sulphur heterocycles are of importance in biological systems. The retrosynthetic analysis will give the synthons. The material required for multi-component reaction will be prepared or purchased depending upon availability. Once the method optimization completes, we will prepare different derivative of that sulphur heterocycle. The prepared heterocycles will be screened for some biological activity. The docking study will be done and active compound will be identified.

National status

In India so many research groups are working on sulphur containing heterocyclic compounds. Among that following are noteworthy contributors-

1. Dr. S. P. Chavan, Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune, Maharashtra.

2. Dr. A. T. Biju, Department of Organic Chemistry, Indian Institute of Science, Bengaluru, Karnataka

3. Dr. J. S. Yadav, Organic Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, Telangana.

4. Dr. Bapurao B. Shingate, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada university, Aurangabad, Maharashtra.

International status

Number of groups is working in the field of sulphur containing heterocyclic compounds. Following are some research groups are making important contribution in this field at international level –

1. Prof. Dr. Guigen Li, Department of Chemistry and Biochemistry, Texas Tech University, Lubbock (USA)

2. Prof. Dr. Shu-Jiang Tu, School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou 221116, Jiangsu, (P. R. China)

3. Prof. Armin de Meijere, Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany

4. Prof. Velentine G. Nenajdenko, Moscow State University, Department of Chemistry, Leninskie Gory, Moscow 119992, Russia

Study rationale

The process of drug discovery has been ongoing since ancient times, with heterocyclic compounds emerging as leading contenders in the pharmaceutical industry over the past few decades. In this study, sulphur heterocycles will be produced through both two-component and multi-component synthesis methods. These synthesized sulphur heterocycles will undergo screening for efficacy against various diseases, with molecular docking studies also being conducted to optimize their activity.

Research methodology

- Retrosynthetic study for sulphur containing heterocyclic compounds will be done and possible routes for target compounds will be designed and will be executed.
- The proposed synthesis of sulphur heterocycle will be designed considering the green chemistry principles.
- The synthesized materials will be sent for characterization to national level institutes.
- The characterization techniques such as 1H NMR, 13C-NMR, Mass spectra, IR spectra will be used to assign the structure of synthesized compound.
- The characterization data will be interpreted and possible structure will be assigned.
- The characterized compounds will be sent to collaborators for biological activity.
- After biological activity of synthesized compounds, the structure activity relation-ship will be predicted.
- The results will be published in international repute journal.

Plan of proposed work:

- 0 to 6 months literature survey.
- 7-17 months procurement of chemicals, glassware and minor instruments required for research.
- 7 to 10 months synthesis of building blocks required for multi-component reactions.
- 7 to 24 months multicomponent synthesis of sulphur containing heterocyclic compounds.
- 12 to 30 months characterization of synthesized material.
- 15 to 30 months bio-evaluation of characterized sulphur heterocycles.
- 25 to 36 months compilation of data
- 25 to 36 months research articles writing
- 30 to 36 months thesis writing
- 24 to 36 months presentation of research work in National/International conferences.

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